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The effect of special packaging on the medication compliance of hypertensive patients

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The Effect of Special Packaging on the Medication Compliance of Hypertensive Patients

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Abstract

This study tested the effectiveness of special packaging in increasing the medication compliance of hypertensive patients in the outpatient clinic at San Joaquin General Hospital. Seventy patients were randomly assigned to an experimental and control group. After a 6 week treatment period, the mean compliance estimates for the experimental and control groups (x_1 = 68.59%, x_2 = 48.67%) were compared and found to be significantly different ($t = 2.46$, $df = 33$, $\underline{p} < .05$). In addition, a statistically significant negative correlation was found between compliance and blood pressure ($r = -0.51$, $\underline{p} < .01$).

Medication compliance, "the extent to which the patient's behavior coincides with the clinical prescription" (Fletcher, Pappius, & Harper, 1979, p. 635), is the crucial link between the doctor's prescription and the healing process. If patients ingest a reduced amount of the prescribed medication the treatment goal may either not be achieved or may be achieved more slowly (Kaplan, 1980). Overdosing on medication is also undesirable since "many medications carry greater risks from overdosage than underdosage" (Rudd, 1980, p. 866). While underconsumption of medication has received more attention in the compliance literature, overconsumption of medication has been estimated to account for 65% of the problems in medication compliance which come to a physician's attention (Swinyard, 1980). Thus, in any discussion on medication compliance it is useful to reiterate that both underdosing and overdosing are to be viewed as a deficit in compliance.

This paper on medication compliance will first present a brief literature review on the subject. A proposed experiment designed to test the effectiveness of special medication packaging on increasing medication compliance in hypertensive patients follows.

Magnitude of Noncompliance

Estimates of how many people are noncompliant range from 11% to 93% (Shope, 1981) with 50% considered typical (Sackett & Snow, 1979, Chap. 2). The wide variability in

the estimates is caused in part by the different operational definitions used for compliance (which vary based on the percentage of compliance necessary for a particular medication to work in a particular disease). For example, in studies on hypertension, patients are classified as compliant when 80% of their pill taking behavior coincides with the doctor's advice. However, in the case of diabetes, administration of insulin must concur 95% of the time with the prescription for the blood sugar level to remain under control. Other factors which are responsible for the variability in compliance estimates include the measures of compliance used (e.g., self report, pill count, laboratory tests) and conceptual problems with respect to setting the cut off point between compliance and noncompliance. For example, when a physician prescribes the minimum dosage required for therapeutic effects to occur, a high degree of medication compliance is more important for the underdosing patient than when the physician prescribes more liberally.

Complications of Noncompliance

Medication noncompliance can not only thwart the health benefits achieved by accurately following a proper medication prescription, but can also lead to inappropriate medication or surgical recommendations and unnecessary testing by physicians who think their treatment recommendations are not working. In addition, in the case of antibiotics, insufficient use may lead to the development

of a strain of organisms which is resistant to the antibiotic (Matter, Markello, & Yaffe, 1974).

Measures of Compliance

Direct Measures

Analysis of body fluids is the most direct and perhaps the most accurate way to measure compliance. Even so, there are problems with this method (Gordis, 1979, Chap. 3). First, there are technical problems with respect to a test's sensitivity and specificity to the presence of the relevant medication, its metabolite, or a marker (an inert substance added to the medication specifically for the detection of compliance). The test may either not be sensitive to or may not pick up the presence of the compliance indicator, or it may lack specificity to the compliance indicator and give a false positive. Second, in carrying out a test, it is important to know the absorption and excretion pattern of the drug in question so that the test is conducted during the critical time for compliance detection.

Body fluids studied to date for use in compliance detection include blood, urine, saliva, sweat, semen, and tears (Litt & Cusky, 1980). While blood is useful in the detection of medication compliance for anticonvulsants, salicylates (e.g., aspirin), digoxin, and theophyllin (for asthma), its use is limited because of the necessity to use invasive venipuncture techniques which are painful, time consuming, require the presence of the patient in the

doctor's office, and carry the possibility of introducing an infection. For these reasons increasing attention has been paid to the alternative body fluids such as urine and saliva.

Because of the high cost of quantitative analysis of body fluids qualitative analyses have become popular. For example, mefenamic and flufenamic acid (to treat arthritis), and riboflavin (a vitamin marker) fluoeresce when present in urine exposed to ultraviolet light. While the use of six mg. of riboflavin as a marker added to each capsule of medication seems promising, Scoutter and Kennedy (1974) caution against its indiscriminate use. First, false positives may be obtained in persons who take multivitamins. Second, testing for the presence of a marker does not indicate the degree of medication compliance. Third, Scoutter and Kennedy point out that a noncomplying patient may happen to take medication right before the body fluid collection while a usually compliant patient may forget to do so. In addition, riboflavin is so readily absorbed and excreted by the body that if riboflavin is to be detected in the urine, the urine should be inspected within two to three hours after the riboflavin is ingested. Finally, riboflavin can change the bioavailability of the medication to which it is added. Thus, many pharmacists advise against the use of riboflavin as a marker.

Indirect Measures

The most commonly used indirect measures of compliance

are pill counts, self reports, outcome assessments, and physician estimates. When combined, these measures are thought to provide as much information as the more direct measures (Litt & Cusky, 1980).

Pill count. The pill count measure of compliance involves the comparison between the number of pills remaining in the patient's bottle and the number of pills that should have remained. Compliance is reported as the number of pills removed during a specific time period divided by the number of pills prescribed for that time period times 100%. Problems encountered with this approach include pharmacist's errors in the filling of the prescription (Monson & Bond, 1978), underdosing patients throwing away pills in anticipation of the pill count, and patients forgetting to make their medication containers available for the pill count. Studies which have investigated the accuracy of pill counts indicate that pill counts overestimate medication compliance by as much as 10% (Bergman & Werner, 1963; Roth, Carson & Hsi, 1970).

Self report. Several investigators have compared self reports with pill counts and urine tests. Feinstein, Wood, Epstein, Taranta, Simpson, and Turskey (cited in Gordis, 1979, Chap. 3) compared interview and pill count estimates of compliance in penicillin prophylaxis treatment (to prevent rheumatic fever). Although both measures had high agreement with respect to classifying patients into the poor compliance groups, there were marked differences in their

classification of patients into good and questionable compliance groups. The interview method overestimated the number of patients classified as having good compliance by 18%. Chaves (cited in Gordis, 1979, Chap. 3) found negative urine tests in 27% of the patients who said they took their pills. In 1970, Rickels and Briscoe compared 675 self reports with pill counts and again found that self reports overestimated compliance. The discrepancy between self reports and pill counts was greatest for subjects who were only slightly noncompliant. Sheiner, Rosenberg, Marate, and Peck (1974) found that average outpatients took only 72% of the digitalis tablets they reported they had taken.

The advantages of using self report include (a) it is cheap, (b) those who admit noncompliance rarely lie, (c) if the only purpose of the interview is to identify noncompliance, many will be identified, and (d) patients who admit to their noncompliance during an interview respond best to interventions (Litt & Cusky, 1980).

Outcome Assessments. While it is natural to assume that compliance to a properly prescribed drug therapy will result in a positive outcome, there are many variables besides the drug therapy which may affect the outcome (e.g., reassurance, stress, sleep, weather, physical health, strength of virus or bacteria, and severity of illness, to name a few). Therefore, compliant patients may sometimes fail to improve promptly while noncompliant patients may improve anyway. This has been demonstrated by Lowenthat,

Briggs, Mutterperl, Adelman, & Creditor (1976). Only 44% of the compliant patients achieved controlled blood pressure whereas 56% of the compliant patients did not. Furthermore, 16% of the noncompliant patients achieved blood pressure control despite their lack of compliance.

Gordis (1979) also notes that "the effect of noncompliance is highly dependent upon how closely the prescribed dosage approximates the minimum dosage required for optimal therapeutic effect....If for example the prescribed dosage substantially exceeds the mimimum effect dosage, low compliance may not reduce effectiveness at all" (p. 34).

Physician estimates of compliance. While it may seem logical to assume that experienced physicians would be adept at estimating their own patients' compliance, studies have shown that this assumption is false. Charney, Bynum, Eldridge, Frank, MacWhinney, McNabb, Scheiner, Sumpter, and Iker (1967) showed that pediatricians' predictions of compliance were no better than chance. Caron and Roth (1968) found that 46% of physicians overestimate compliance. They noted that the senior physicians were no better at predicting than the junior physicians who in turn were no better than the residents. Davis (1966) found that medical students were indeed better at predicting noncompliance than attending physicians.

Determinants of Compliance

Features of the disease

Disease characteristics are considered unimportant as determinants in compliance (Haynes, 1979, Chap. 4). Less than half of the disease factor studies that Haynes, Taylor & Sackett (1981) reviewed found significant correlations between disease factors and compliance level. The exceptions to these are: (a) that psychiatric patients tend to be low compliers, (b) the more numerous the symptoms possibly the lower the compliance, and (c) increased disability may be accompanied by increased compliance.

Clinical Setting and the Referral Process

Because attendance at the physician's office and medication compliance are related, it is helful to look at features of the referral process and clinical setting which help the patients to keep their physician's appointments. Although there is lack of research in both areas, several helpful factors have been determined; (a) the longer the time between the referral and the appointment, the lower the chances are that the patient will keep the appointment (Haynes, 1979, Chap. 4), (b) Hoening and Ragg (cited in Haynes, 1979, Chap. 4) found that patients referred to a psychiatric clinic were more likely to keep their appointment if the referral was to a specific physician, and (c) decreasing the waiting time in the clinic may increase clinic attendance (Rockart & Hoffman, 1969).

Features of the Regimen

Getting patients to keep their clinic appointments will not necessarily increase medication compliance. There are several features of the treatment regimen which also affect medication compliance (Haynes, 1979, Chap. 4). They are as follows;

(1) Duration of treatment. Numerous studies have shown that the duration of treatment is accompanied by a concomitant decrease in medication compliance (Haynes, 1979, Chap. 4).

(2) Complexity. Studies almost unanimously indicate that the greater the number of medications prescribed the lower the compliance (Haynes, 1979, Chap. 4). However, the influence of the frequency of medication in the medication regimen is not as well understood. Some studies have indicated that as the frequency of taking medication increases from once a day to four times a day, the medication compliance decreases. Other studies have failed to support this observation (Haynes, 1979, Chap. 4).

(3) Side effects. Intuitively speaking, I would expect that the greater the number of side effects of taking a drug the lower the compliance would be. While some studies which cite data for psychiatric patients support this contention, the majority of studies have provided evidence which refute it (Haynes, 1979, Chap. 4). For example when patients have been asked to list their reasons for noncompliance, side effects are mentioned only 5% to 10% of the time, and even

then they are mentioned towards the bottom of the list. This finding indicates that while side effects may be important when they occur, they are not the most common cause of noncompliance.

(4) Cost. Most studies have demonstrated a negative relation between cost and compliance, although a few have found no correlation or a positive one (Haynes, 1979, Chap. 4).

(5) Dispensing. Haynes (1979, Chap. 4) describes a controlled study which was carried out on the effects of the safety lock on pill containers with respect to compliance. The data showed that the safety lock significantly reduced medication compliance. Many who did comply reported that they had removed the safety container top.

Mattar, Markello, and Yaffe (1975) found that community pharmacists, when filling prescriptions, dispensed less medication than was prescribed on 15% of all prescriptions for an antibiotic for otitis media.

Patient characteristics

(1) Demographics. Studies have generally shown that knowledge of a patient's demographic characteristics does not help to predict medication compliance (Mathew & Hingson, 1978).

(2) Knowledge. While knowledge about a medication regimen and disease is helpful, it is not in and of itself sufficient to insure compliance (Bergman & Werner, 1963; Sackett, Haynes, Hackett, Taylor, Gibson, Roberts, &

Johnson, 1975). Sackett et al. (1975) conducted a study on steel workers with newly discovered hypertension in a Canadian factory. The hypertensive workers were divided into a group which received special instruction concerning hypertension and its treatment and a group which did not receive any special instruction. While the group members which received special instruction concerning hypertension scored higher on a quiz testing knowledge about hypertension, they were not found to be more compliant than the group receiving no special instruction.

(3) Health belief model. According to the health belief model the probability patients will follow medical advice is a function of the patients' perceived susceptibility to the disease, the perceived severity of the disease, and the perceived benefits and barriers related to compliance. The model also includes other variables (such as motivation, physician-patient interaction, characteristics of the regimen, etc.) as influential on compliance (Hershey, Morton, Davis, & Reichgott, 1980). Several studies testing the model have shown positive correlations up to .5 and .6 between the patients' health beliefs and feelings and their compliance (Becker, Maiman, Kirscht, Haefner, Drachman, & Taylor, 1979, Chap. 6). The correlations tend to be higher when the health beliefs are compared with concurrent rather than subsequent medication compliance, which may suggest a bidirectional relationship between the two variables. That is, patients' beliefs may

affect their medication compliance and compliance may influence beliefs.

(4) Locus of control. Locus of control refers to the way a person views the events which occur in his/her life. Persons with an external locus of control believe that whatever happens to them is due to chance, luck, fate, or some outside power. On the other hand, persons with an internal locus of control believe they are in control of what happens (Duke & Cohen, 1975). Several studies have supported the contention that internal locus of control is significantly related to compliance (Hershey, et al., 1980; Duke, et al., 1975, Becker, et al., 1979) although more studies need to be conducted.

(5) Disease denial and rationalization. Podell and Gary (1976) suggest that denial or rationalization of a medical condition is related to medication noncompliance in hypertensive patients. In their study half of the patients who failed to take their medication or go to their physician appointments presented illogical excuses such as "I knew my blood pressure was high so I did not keep my appointment."

Features of the Doctor-Patient Interaction

Several features of the doctor-patient relationship have been studied, some of which have been shown to have a significant impact on patient compliance. Patients' overall satisfaction with their care has been repeatedly demonstrated to have a positive relation to compliance (Daly & Hulka, 1975). When patients' expectations are met, they

are more likely to comply (Shope, 1981). As the level of medication supervision increases medication compliance increases (Haynes, 1979, Chap. 8). Other variables which may be related to compliance include the patient's belief in the physician's ability and the patient's perception of the physician as friendly (Shope, 1981).

Strategies For Improving Patient Compliance

There have been several strategies proposed to improve patient compliance. Before initiating an attempt to improve medication compliance however, Albert Jonsen (1979) suggests that the experimenter be able to verify that the following guidelines have been met; (a) the physician's diagnosis is correct, (b) the drug therapy will do more good than harm to the patient, and (c) the patient is an informed and willing participant.

Patient Education

(1) Disease and treatment. Theoretically one would hypothesize that patient education would increase medication compliance. Research has shown, however, that patient education is not a sufficient condition for medication compliance to occur (Haynes, 1979, Chap. 8).

(2) Medication regimen. Patient errors in medication can be subdivided into (a) faulty comprehension of medication regimen accompanied by medication errors, and (b) good comprehension of medication regimen accompanied by medication errors. Because studies indicate that medication errors are frequently accompanied by faulty comprehension of

the treatment regimen, it would behoove the health care provider to carefully explain the treatment regimen itself, to perhaps provide written instructions of the schedule (Podell, et al., 1976; Blackwell, 1979), and to ask patients to explain the treatment as they understand it to validate their comprehension of the treatment.

Drug Regimen

Another way to decrease faulty comprehension is to simplify the medication itself by reducing the number of different medications used and reducing the frequency of the medication administrations. Studies which have compared the efficacy of the different dose frequencies have all indicated that the less frequent regimens are as effective as the more frequent regimens (Blackwell, 1979). However, recent work in juvenile onset diabetes mellitus indicates that frequent administration of insulin might be advantageous due to its superior control of blood sugar levels (Davidson, 1981).

While it is a common belief that the larger, less frequent doses of medication are accompanied by more side effects, this has not been supported in the literature to date (Blackwell, 1979, Chap. 9). Caution and discrimination should nonetheless be observed in prescribing larger doses, and side effects should be monitored.

Tailoring

Although tailoring has not been studied as an effective variable in and of itself, it intuitively would seem that

tailoring a medication to a patient's own schedule would increase compliance. For example, Podell and Gary (1976) suggest scheduling the ingestion of a diuretic during the time of day the patient will have a bathroom at his disposal. Norell (1979) found that medication compliance was greatly improved in subjects who were given an education and medication tailoring program.

Parenteral Drug Administration

Numerous studies have shown that whenever injections can be given by the health care provider, patient compliance increases (Haynes, 1979, Chap. 8). The low rate of compliance found in diabetics who are prescribed daily injections of insulin underscores the importance of the health care provider's role in the drug administration rather than the injection itself.

Extended Supervision

The concept of extended supervision involves such things as frequent clinic visits, making home visits, using outreach clinics to reach those who might otherwise fail to go to the doctor, and adding an extra person to the health care team to supervise the patients' use of their medications.

Many studies demonstrate the effectiveness that extended supervision has on medication compliance, though it is difficult to separate the effects of supervision from patient education and counseling (Haynes, 1979, Chap. 8).

Patient Involvement and Behavior Modification

Such behavior modification techniques as (a) positive reinforcement, (b) negative reinforcement (Azrin & Podell, 1969), (c) security-deposit contingency contracts, (d) self monitoring (Epstein & Masek, 1978), and (e) contingency management (Lowe & Lutzker, 1979) have been used successfully to increase compliance. Haynes (1979, Chap. 8) comments that while many of these techniques would be difficult and expensive to implement in a private office, they do demonstrate the effectiveness of the principle involved.

Attendance at the doctor's office is positively correlated with medication compliance (Haynes, 1979, Chap. 8). To encourage clinic/office attendance, such procedures as calling patients or sending them reminders of their scheduled appointments have been effective. In addition, reducing the time patients have to wait in the office before they see the physician has also been shown to increase medication compliance (Rockart et. al., 1969).

Medicine Packaging

Special medication packaging works as a discriminative stimulus or cue for appropriate pill taking behavior. Such packages are designed so that patients can see when each pill should be taken and if a particular pill has been taken. One of the most attractive features of this approach is that it is time efficient, i.e. the packaging effects a maximal response to medication compliance with a minimal

intervention. This approach works around such difficult variables to control as physician-patient interaction and relationship, medication regimen, and patients' health beliefs. For these reasons special medication packaging will be used in the proposed study. Several studies have been conducted to determine the effectiveness of special pill containers and daily reminders (Demetral, Gipson, Irwin, Anderson, & Catania, 1981; Eshelman, & Fitsloff, 1976; Gazzar, 1978; Linkewich, Catalano, & Flack, 1973; Rehder, McCoy, Blackwell, Whitehead, & Robinson, 1980). The effectiveness of such special pill containers has been repeatedly demonstrated with psychiatric medications (see Weber, Demetral, Anderson, Gipson, & Catania, 1978, for more information), but research conducted with other disease populations has been inconclusive.

For example, the beneficial treatment effects of the special medication packaging were clearly demonstrated in the short term study conducted by Linkewich, et al. (1973) on penicillin compliance although a second treatment variable, an instruction card, was added to the package. This instruction card could have interacted with the special packaging to enhance its effectiveness.

Eshelman et al. conducted a study with hypertensive patients in 1976. In this study the special medication packaging alone was compared to a control group who received their medication in regular vials. The results were somewhat confusing. While a urine assay indicated that

medication compliance had increased, the pill count showed very little change. There are several possible explanations of what occurred. Most likely (a) the diuretic measured in the urine assay, chlorthalidone, gave an overestimate of medication compliance due to its long half life, (b) several subjects given the special treatment package continued to take their medication out of the vials at least part of the time. If this occurred, medication compliance as measured by the pill count of the special package was underestimated. Thus, an average or summation of the two estimates would probably have yielded the most accurate estimate. When I averaged the results, 65% of the patients receiving their medication in the bottles were compliant versus 78% of the patients receiving their medication in the special packaging. However, when the data was submitted to a chi square analysis the difference between the two group's proportions of compliant patients was not statistically significant. Thus, the special medication packaging was not shown to increase medication compliance in this case.

Rehder et al. (1980) conducted a three month study on hypertensive patients. One hundred subjects were assigned randomly to one of four groups: (a) the control group, (b) the disease and medication counseling group, (c) special medication container group, and (d) the special medication container and counseling group. Compliance was measured by a pill count. A problem with the study was that only 64% of the patients who kept their pharmacy appointments brought in

their pill containers for a pill count. It would seem likely that the patients who brought their pill containers in would tend to be the most compliant in taking their medication. It is not surprising, then, that the medication compliance estimate obtained by the pill count was very high across all four treatment groups (greater than 85%), and that there were no significant differences between treatment groups. However, when the percentage of patients who had greater than 95% medication compliance was compiled for each group, the counseling and special medication container group and the special medication container alone group had a significantly greater proportion of 95% compliance patients than either the counseling alone or control groups. In this study the subjects' blood pressures in each treatment group were also noted. That blood pressure changes did not reflect the differences in medication compliance is not surprising since once a patient is over 80% compliant in the ingestion of antihypertensive medication, other variables are considered to be more important in lowering blood pressure (such as salt intake and amount of antihypertensive medication prescribed).

Thus, while the effectiveness of the special medication packaging has been demonstrated with psychiatric medications, its effectiveness with nonpsychiatric populations needs more empirical support. A nonpsychiatric population of particular interest is the hypertensive population.

Hypertension

Hypertension (high blood pressure) is a serious disorder which affects 15% to 25% of adults in the United States (Williams, Jagger, & Braunwald, 1980). There are four plausible end-organ effects associated with hypertension if left untreated: (a) kidney failure due to glomerularsclerosis (scarring of the glomerula in the kidneys which filter poisons out of the blood), (b) heart failure due to left ventricular hypertrophy, (c) cerebral hemorrhage, (d) atherosclerosis which may lead to a myocardial infarction or a stroke.

Medications used to treat hypertension are divided into three classes or "steps", with each step associated with increasing risks for side effects. Step I medications include diuretics and are the treatment of choice of a person with newly discovered hypertension or borderline hypertension. If a step I treatment does not lower the blood pressure enough, step II drugs such as beta blockers and central acting drugs are added. Finally, if neither step I or step I and step II drugs used together are sufficient, a step III treatment, vasodilators, may be tried in addition to the step I and step II drugs. Vasodilators reduce blood pressure by acting directly on the constricted vessels thereby expanding them so as to reduce the pressure.

While properly prescribed and taken antihypertensive drug therapy is usually effective in reducing blood pressure, noncompliance is a common problem. For example,

in Sackett's 1975 study conducted on hypertensive steel workers he and his associates found that only 48% of the patients in the control group were compliant in taking their medications. Only 53% of patients receiving extensive training on hypertension and its treatment were classified as compliant at the end of the six month experiment. Sackett et al. concluded that instructional strategies "involving more direct attempts of behavior modification" were more likely to be successful (p. 1207). Lowenthal, Briggs, Mutterperl, Adelman, and Creditor (1976) found that 50% of the patients in their study were compliant.

Explanations of low compliance in hypertensives include (a) hypertensive patients are usually asymptomatic and thus have difficulty believing that they are "sick" and need to take medication, (b) the medication is expensive, (c) the medication has potential side effects which range from dizziness, weakness, and headaches, to depression, potassium depletion, and exacerbation of asthma and heart failure (Williams, Jagger, & Braumwald, 1980), (d) the medication does not cure the cause of hypertension - thus patients are put on a long term drug regimen indefinitely, (e) patients on more complex drug regimen get confused with respect to when to take each medication, (f) patients forget if they have taken their medications. Each of these explanations for noncompliance has been discussed earlier in the paper (see pp. 8-12).

What remained to be shown is that special medication packaging could indeed increase medication compliance in hypertensive patients. The special medication packaging works as a discriminative stimulus or cue for appropriate pill taking behavior. To this end the packages are designed so that the patient can see when each pill should be taken and if a particular pill has been taken. Because of its form the special packaging addresses two of the previously mentioned explanations for medication noncompliance - when to take the pills and if a particular pill has or has not been taken.

To adequately demonstrate the effectiveness of the special medication packaging, a study was carried out that controlled variables which might either challenge the study's internal or construct validity or otherwise make the results of the experiment hard to evaluate. The following suggestions were integral to the study described throughout the rest of the paper:

(1) Select a group of hypertensive patients who are judged to be capable of self administration of medication.

(2) Where applicable, prescribe hydrochlorothiazide (HCTZ) or dyazide to patients who need to take a diuretic because the thiazides are easily detected in the urine. Hydrochlorothiazide is preferred over chlorthalidone because it has a shorter half life (2.5 hours versus 44 hours). Thus detection of its presence in the urine indicates that the medication was ingested within the previous 24 hour

period. On the other hand, the presence of chlorthalidone indicates that medication has been ingested within the past 48 to 72 hours. Because the antihypertensive medication regimen is a daily one, hydrochlorothiazide gives a more accurate estimate of medication compliance (Benet & Sheiner, 1980). Urine specimens should be collected within four hours after the ingestion of the medication to insure the detection of the medication's presence.

(3) Offer the special treatment package alone to an experimental treatment group and compare the medication compliance to a control group whose drugs are dispensed in regular pharmceutic vials.

(4) Use nonreactive routine tests to estimate medication compliance (e.g. urine samples, blood pressures) in order to avoid such reactive patient responses as "the guinea pig effect" (Webb, Campbell, Schwartz, & Grove, 1981, p. 49) where patients change their usual behavior (such as medication compliance) due to their awareness of being observed. By using measures that the patients are familiar with the guinea pig effect can be avoided.

(5) To increase the probability that the patients assigned to the special medication packaging group discontinue using their old pills in the vials, several months before the experiment begins the physicians participating in the study should be asked to prescribe only the number of pills that the patients estimate they need in order to continue taking their medication until the next clinic visit.

Method

Subjects

The 70 patients who qualified to participate in the study were referred by three hospital resident physicians and one staff physician. Criteria for selection included:

(1) an untreated diastolic blood pressure greater than 90 mm Hg or systolic blood pressure greater than 145 mm Hg.

(2) capability to administer medication to one's self.

(3) exclusive use of the hospital pharmacy to fill antihypertensive medication prescriptions.

(4) being a patient of a physician who agreed to follow the guidelines of our study as listed below.

Treatment Conditions

The 70 patients were randomly assigned to the two treatment groups of the posttest-only control group design:

(1) Group I, which received the special pill containers and a posttest.

(2) Group II, which received the regular pill containers and a posttest.

Patients were assigned so that each group would have approximately the same number of patients receiving Step I treatment (only diuretics), Step I & Step II treatments, and Step I, II, and III treatments. All patients were seen by their doctor on at least one occasion prior to the beginning of the study. After repeated rescheduling of clinic appointments we were able to get only 48 patients to come to

the first clinic appointment of the study. Of these 48, 72.9% or 35 came to the second scheduled clinic appointment. The second clinic visit was not rescheduled if missed because the number of pills prescribed during the first visit matched the number of days between the scheduled appointments. Thus, pill counts and urine assays would necessarily be affected by an extension between the first and second clinic visits.

The demographic characteristics of the 35 patients who remained in the study are similar to those who dropped out (see Table I for a comparison). About a third of the patients were white, a third black, and a third were of Mexican or Oriental descent. About a third of the patients were married, about a fourth were widowed, and the remaining patients were single, separated, or divorced. Only 2 of the 35 patients' expenses were covered by a third party (i.e. insurance). Nine patients were classified as private (i.e. having no funding other than their own) and 24 patients' medical expenses were covered by government sources (i.e. Medi-Cal and Medi-Care). The patients who remained in the study did not differ significantly with respect to demographic characteristics from the subjects who dropped out.

Of the 35 patients lost in the study it is known that one was hospitalized for a myocardial infarction, another was hospitalized for coronary bypass surgery, two moved out of town, three were misrouted to other physicians, two

Table I. Summary of Demographic Characteristics of Study Subjects versus Drop Out Subjects and Experimental versus Control Subjects

Demographic Characteristics		Study Subjects N=35	Drop Out Subjects N=35	Experimental Subjects N=14	Control Subjects N=21
Age	Mean	59.77	54.80	58.79	60.43
Standard Deviation		14.53	13.33	15.03	14.53
Race	White	11	14	3	8
	Mexican	5	8	3	2
	Black	14	12	7	7
	Oriental	5	1	1	4
Marital Status	Single	4	4	2	2
	Married	14	18	7	7
	Widow	9	5	4	5
	Separated	2	4	0	2
	Divorced	6	4	1	5
Payment	Medicare	3	1	2	1
	Medicare/ Medi-cal	11	6	4	7
	Private	9	11	3	6
	Medi-cal	10	15	4	6
	3rd Party	2	2	1	1
Doctor	Young	18	15	8	10
	Formoso	4	4	2	2
	Vaughan	6	12	2	4
	Renal	7	4	2	5
City	Stockton	30	21	12	18
	Lathrop	0	1	0	0
	French Camp	0	3	0	0
	Galt	0	1	0	0
	Linden	1	0	1	0
	Tracy	1	1	1	0
	Manteca	2	4	0	2
	Lodi	1	4	0	1

patients became angry and left before seeing their physician after waiting in the clinic office for over an hour, and one experimental patient was mistakenly given her medication in vials at the pharmacy.

Of the 35 subjects who were followed throughout the study, 14 were in the experimental group and 21 were in the control group. As can be seen in Table I, the demographic characteristics are approximately equivalent between the experimental and control groups.

Special Pill Containers

The special pill containers were equivalent to the Medi-Dose containers used by Demetral et. al., (1981) in their study on medication compliance. The prescribed anti-hypertensive pills were placed individually in plastic compartments on medication cards clearly labelled for the time of day each pill should be taken. There was a new medication card or container for each day of the regimen, and these pill containers were given to patients in the correct order of their intended use. It should be noted here that special medication packaging has been described as difficult to open (Eshelman & Fitzloff, 1976). Thus the special medication packages probably did not enjoy an unfair advantage over the safety-cap prescription vials with respect to the ease in which the containers were opened.

Procedure

Physician guidelines.

(1) The patients' second clinic appointment was six

weeks after the first appointment.

(2) Medication prescriptions covered the six week interval between clinic visits.

(3) If the patient was on a beta blocker, the patient's pulse was taken at the final clinic appointment.

(4) Urine samples were collected on the day of the second clinic visit.

(5) Special medication packaging patients were told that their antihypertensive medication would be dispensed in different containers and that the patients should temporarily discontinue their "old" medication.

(6) All patients were reminded to bring in their medication on their next scheduled visit. The reminder came in the form of telling the patients not to forget and giving the patients a written reminder with the date of the next scheduled visit.

Pharmacist guidelines. Patients in the control group received their medication as usual in the safety-cap prescription vials from the hospital pharmacists. As is customary, the hospital pharmacists briefly explained the medication regimen (i.e. read the vial label). Patients in the special medication container group received their medication at the hospital pharmacy in the special medication packages with the same explanation of the medication regimen (i.e. read the label). In addition, the

pharmacists briefly explained how to use the packaging. In order for the experiment to have high internal validity (which means that the experimental results are due to the manipulation of the treatment variables), both the special packaging group and the control group received the same treatment in all respects as much as possible, except for the special packaging. Thus the pharmacists gave the control group the same amount of time and attention as they gave to the special packaging group.

The pharmacists were requested to be brief and nonjudgmental in their explanations concerning the new packages and to explain that the hospital was just trying them out. Giving additional information was avoided.

Nurse guidelines. The nurse completed her routine duty of taking each patient's blood pressure before the patient saw the doctor. In addition, the nurse requested the patients to provide her with a urine sample while they were waiting in the clinic to see the doctor.

Dependent Measures of Compliance

Medication compliance was estimated by the following measures:

(1) presence of hydrochlorothiazide in the urine

(2) resting pulse at clinic visits for patients taking beta blockers

(3) the blood pressure reading at clinic visits

(4) the pill count at each clinic visit

(5) the blood pressure reading at any emergency room visit during the study period

A special attempt was made to use nonreactive measures as recommended by Webb, Campbell, Schwartz, and Grove (1981) so that the estimates of compliance would be more accurate. The raw score obtained on each measure for each subject was assigned the number of points suggested by a table of weighted scores which was constructed before the study began (see Appendix A for the listing). One dependent measure was dichotomous (the presence or absence of medication in the urine) while other measures estimated several levels of compliance. Each subject was assigned a percentage compliance score by adding up the total number of points earned and dividing that sum by the total number of points possible for that individual. Once each subject was assigned a score, the mean percentage compliance score and standard deviation for all the subjects was calculated and the mean percentage compliance scores for the special packaging treatment group and the control group were compared with a t-test. In addition the means for each individual compliance measure were compared using the raw scores when possible.

Detection of medication in the urine. Lowenthal, Briggs, Mutterperl, Adelman, and Creditor (1976) describe a test for the detection of thiazide diuretics (such as hydrochlorothiazide and dazide) in the urine which yields qualitative results (i.e. the presence or absence of the

drug rather than quantity). Urine specimens of patients who are prescribed thiazides were subjected to this test and were scored as follows: for the detection of any amount of thiazide in the urine, 10 points were assigned.

Resting pulse. If blood pressure control is not achieved by diuretics alone, beta blockers (a step II treatment) may be added. The beta are receptors of the beta part of the sympathetic nervous system. There are beta receptors located in the heart. When these are stimulated, there is an increase in heart rate and ultimately an increase in the blood pressure. The role of the beta blockers, then, is to block the beta receptors from responding to stimulation by the sympathetic nervous system and thus slow down the heart rate and decrease the blood pressure. The beta blocker propranolol was used in this study. The resting pulse of patients taking beta blockers was measured at the second clinic visit. If it was less than 80 beats per minute, the patient received 8 points. If it was between 80 and 90, 4 points was assigned. If it was greater than 90, no points were assigned.

Blood pressure. The blood pressure was also measured at each clinic visit as an indication of the patients' medication compliance. While this measure, as discussed earlier, is far from perfect, successful blood pressure control is indicative of medication compliance and an extremely high blood pressure (greater than 110 diastolic or 190 systolic) is indicative of noncompliance. The scoring

for this measure can be found in Appendix A.

Pill count. The pill count measures of compliance involves the comparison between the number of pills remaining in the patient's bottle and the number of pills that should have remained. Consumption is reported as the number of pills removed during a time period being measured divided by the number of pills prescribed for that time period times 100%. See Appendix A for scoring.

Emergency room visits. During the study period we expected that some of the patients in our group would visit the emergency room in regards to a minor medical problem. Since it is routine at the emergency room to have one's blood pressure measured and recorded upon requesting treatment, we decided that in the event that some of our study patients would visit the emergency room we would obtain and use their blood pressure as a nonreactive measure of compliance. We believe that the emergency room blood pressure was more likely to reflect the true degree of compliance than the clinic blood pressure because underconsumers could not easily "prepare" for an emergency by abruptly taking their medications as they might for a routine clinic visit. The scoring of the blood pressure readings taken at the emergency room was somewhat different than the clinic blood pressure readings since emergency room visits by nature are more stressful, and therefore more likely to elevate blood pressure. See Appendix A for the actual scoring.

Results

The combined measures of compliance indicate that the experimental group $\overline{X}$ = 68.59% was more compliant in taking medication than the control group $\overline{X}$ = 48.67% ($t = 2.46$, $df = 33$, $p < .05$). This difference of 20 percentage points is a 42% improvement in score. Although most individual measures of compliance suggest that the experimental group was more compliant than the control group, none of the individual measures of compliance were able to differentiate the experimental group from the control group at a statistically significant level. The mean values for each of the measures used are presented in Table II.

Because the purpose of antihypertensive medication is to lower blood pressure, this measure of compliance was examined more closely than the other measures.

A statistically significant negative correlation was found between the combined compliance measures (minus the blood pressure measure) and the combined systolic and diastolic blood pressure of all the subjects ($r = -0.51$, $p < .01$). However, no statistically significant difference was found between the experimental and control groups' blood pressure (combined or diastolic) at the end of the six week treatment interval.

Over the six week treatment interval the experimental groups' combined blood pressure ($\overline{X}_1 = 232.71$, $\overline{X}_2 = 229.07$) dropped an average of 3.64 points per person while the control group's combined blood pressure reading ($\overline{X}_1$ =

Table II. Summary of Individual and Combined Estimates of Medication Compliance in the Esperimental and Control Groups

	Experimental			Control		
	n	$\bar{x}$	s.d.	n	$\bar{x}$	s.d.
Individual Measures						
Clinic Blood Pressure						
combined systolic and diastolic (mm Hg)	14	229.07	23.05	21	228.67	28.33
diastolic (mm Hg)	14	83.36	8.59	21	84.57	10.66
Pulse (beats per minute)	7	68.86	8.13	6	75.17	13.24
Pill count (percent of pills taken)	12	96.42%	4.73%	9	81.33%	30.68%
Urine (+ denotes detection of HCTZ)	9	2 samples +		15	2 samples +	
Emergency room blood pressure						
systolic (mm Hg)	3	123.33	14.27	0	---	---
diastolic (mm Hg)	3	75.33	3.77	0	---	---
Overall Percent Compliance Estimate (Combined Measures)	14	68.59%	18.56%	21	48.67%	26.13%

224.19, $\overline{X}_2$ = 228.67) increased an average of 4.48 points per person. These changes in blood pressure were not found to be statistically significant at the $\underline{p}$ = .05 level.

Discussion

The use of multiple measures of compliance has proved useful in this study. While most individual measures of compliance suggested that the special medication packaging increased medication compliance, no measure alone demonstrated a statistically significant difference between the experimental and control groups. By combining a variety of measures we were able to approach the construct of compliance from several angles and thus obtain a more accurate estimate of the true compliance rate of each group.

Just as data on individual subjects in an experimental and control group do not always point to the general pattern of results, the data we obtained on the individual measures of compliance varied from the general pattern which emerged when data from all the measures were summated. The pill count provided a maximum estimate of compliance whereas the urine assay provided a minimal estimate. This occurred because each individual measure (just as each individual patient's data) is subject to error. The pill count was likely an overestimate of compliance due to it's reactive nature (asking the patients to bring the pills in and providing them with a written reminder). Other possible errors include the pharmacist dispensing the prescription as

requested, the experimenter counting the pills accurately, and the most compliant patients "remembering" to bring their pills in. A different type of error is hypothesized to have affected the detection of HCTZ in the urine. In an effort to obtain a nonreactive measure of compliance, patients were not warned ahead of time that a urine sample would be taken at the second clinic visit. Instead, nurses requested the samples as soon as the patient reported to the clinic on the day of their second appointment. However, most patients voided minutes prior to checking in. Since the half life of HCTZ is 2.5 hours, and patients were scheduled to check in approximately four hours after ingestion, it was important to obtain the earliest urine sample possible. Patients who voided just prior to the clinic visit had probably excreted most of the medication. Thus, when the nurses requested urine samples, there was little medication left to excrete. Another possible source of error includes the sensitivity of the HCTZ detection test: The test we used may not have picked up the presence of HCTZ.

Though blood pressure was negatively correlated with compliance across all subjects, there was no statistically significant difference found between the blood pressure measures or changes in measures in the experimental and control groups. Several reasons are postulated:
(1) all subjects had been receiving treatment for hypertension when the study began (i.e. no newly discovered patients began with out study). Therefore, most patients'

blood pressure in both groups were already under fair control at the beginning of the study.
(2) factors other than compliance may affect blood pressure (e.g. appropriateness of drug, the dosage level, and diet).
(3) A period of six weeks may not be of sufficient duration for the blood pressure to fully respond to the increased rate of compliance caused by the special packaging.
(4) A sample size of n = 14 experimental subjects may have not provided enough power to detect the effect that increased medication compliance has on blood pressure.

An attempt was made to use nonreactive measures in this study. All measures with the exception of the pill count appeared to meet this goal (no one questioned the reason why any measure was taken with the exception of the pill count). When patients were requested to bring their pills to the second clinic appointment of our study, many asked why. Several comments indicated that the patients knew why we wanted them to return with the pills (e.g. "You want to see if I take my pills, huh?"). Since the pill count was so reactive it is not surprising that of all the compliance measures the pill count gave the highest estimates for both the experimental and control groups.

This study has demonstrated the effectiveness of the special medication packaging in increasing compliance rates in hypertensive patients on a short term basis. New studies need to be carried out which can demonstrate the effectiveness of the special medication packaging on a long

term basis. If the packaging is found effective over a period of several months, it is probable that statistically significant drops in blood pressure in comparison with a control group will result, thus making the cost of packaging justifiable. New populations of subjects (e.g. diabetics, patients with congestive heart failure; private office and family practice patients) need to be studied to demonstrate the effectiveness of the special medication packaging across different medical conditions and settings.

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APPENDIX A

Point system for quantifying the measures of compliance

Measurement	Points
(1) Detection of hydrocholorothiazide in the urine	10
(2) Blood pressure reading at the clinic visit:	
(a) both systolic less than or equal to 145 and diastolic less than or equal to 90	10
(b) both systolic less than or equal to 170 and diastolic less than or equal to 100, but either systolic greater than 145 or diastolic greater than 90 [If both are equal to maximum value (170, 100), score 0]	4
(c) either systolic greater than 170 or diastolic greater than 100 or both equal 170 & 100	0
(3) Resting pulse:	
(a) less than 80 per minute	8
(b) between 80 and 90 per minute	4
(c) greater than 90 per minute	0
(4) Pill count at clinic visit:	
(a) relfects taking better than 90% of medication	10
(b) relfects taking between 80% and 90% of medication	5
(c) reflects taking less than 80% of medication	0

(5) Blood pressure reading at any emergency room visit:

(a) both systolic less than or equal to 145 and diastolic less than or equal to 90 15

(b) either systolic greater than 145 or diastolic greater than 90, but both systolic less than or equal to 160 and diastolic less than or equal to 100 8

(c) either systolic greater than 160 or diastolic greater than 100 but both systolic less than or equal to 190 and diastolic less than or equal to 110 4

(d) either systolic greater than 190 or diastolic greater than 110 0